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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 0305

Application Number: 09/732,439
Filing Date: December 07, 2000
Appellant(s): ANDERSON ET AL.

Robert E. Hanson
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 26, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 26 November 2004 has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The rejection of claim 63 under 35 U.S.C. 101 set forth in prior Office Action mailed 23 August 2004 has been withdrawn in view of Appellant's Amendment of 26 November 2004 submitted under 37 CFR 1.116. The statement also fails to acknowledge the outstanding objection to claim 72 for depending on nonelected claim 66.

(7) Grouping of Claims

The rejection of claims 59-63 and 72-73 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

The rejection of claims 59-63 and 72-73 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

The rejection of claims 61-63 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

The rejection of claims 59-61, 63, 72 and 73 under 35 U.S.C. 102(e) as being anticipated by Verma et al. (U.S. Patent No. 5,639,950, issued June 17, 1997, filed June 29, 1994, having an effective filing date of September 29, 1992), stand or fall together because appellant's brief does

not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

The rejection of claims 59-63 and 72-73 under 35 U.S.C. 103(a) as being unpatentable over Verma et al. (U.S. Patent No. 5,639,950) in view of Rayapati et al. (Plant Physiology, 1989, Vol. 91, pages 581-586) and in light of Applicant's admitted prior art, stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,344,923	Verma et al.	Issued September 6, 1994
6,281,411	Adams et al.	Issued August 28, 2001
5,780,709	Adams et al.	Issued July 14, 1998
5,639,950	Verma et al.	Issued June 17, 1997

HU et al. A bifunctional enzyme (Δ1-pyrroline-5-carboxylate synthetase) catalyzes the first two steps in proline biosynthesis in plants. Proceedings of the National Academy of Sciences, USA, Vol. 89, pages 9354-9358, October 1992.

VERBRUGGEN et al. Osmoregulation of a pyrroline-5-carboxylate reductase gene in *Arabidopsis thaliana*. Plant Physiology, Vol. 103, No. 3, pages 771-781, November 1993.

DOUGHERTY et al. Cloning human pyrroline-5-carboxylate reductase cDNA by complementation in *Saccharomyces cerevisiae*. Journal of Biological Chemistry, Vol. 267, No. 2, pages 871-875, January 15, 1992.

BRANDISS et al. Proline biosynthesis in *Saccharomyces cerevisiae*: analysis of the PRO3 gene, which encodes delta 1-pyrroline-5-carboxylate reductase. Journal of Bacteriology, Vol. 174, No. 15, page 5176, August 1992.

BARNETT et al. Amino acid and protein metabolism in Bermuda grass during water stress. Plant Physiology, Vol. 41, pages 1222-1230, 1966.

WYN JONES AND STOREY, Physiology and Biochemistry of Drought Resistance in Plants, Ch. 9, Betaines, pp. 171-204, Academic Press, Australia, 1981.

MCCUE AND HANSON, Drought and salt tolerance: towards understanding and application. Trends in Biotechnology, Vol. 8, pages 358-362, 1990.

VAN RENSBERG et al., Proline accumulation as drought tolerance selection criterion: its relationship to membrane integrity and chloroplast ultrastructure in Nicotiana tabacum L. Journal of Plant Physiology, Vol. 141, page 1880194, 1993.

RAYAPATI et al. Pyrroline-5-carboxylate reductase is in pea (Pisum sativum L.) leaf chloroplasts. Plant Physiology, Vol. 91, pages 581-586, 1989.

DELAUNEY et al. Proline biosynthesis and osmoregulation in plants. The Plant Journal, Vol. 4, pages 215-223, 1993.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 59-63 and 72-73 are rejected under 35 U.S.C. 112, first paragraph. This rejection was initially set forth in prior Office Action mailed November 19, 2002, and repeated below.

Claims 61-63 are rejected under 35 U.S.C. 112, second paragraph. This rejection was initially set forth in prior Office Action mailed November 19, 2002, and repeated below.

Claims 59-61, 63, 72 and 73 are rejected under 35 U.S.C. 102. This rejection was initially set forth in prior Office Action mailed November 19, 2002, and repeated below.

Claims 59-63 and 72-73 are rejected under 35 U.S.C. 103. This rejection was initially set forth in prior Office Action mailed November 19, 2002, and repeated below.

Claim Rejections - 35 USC § 112

Claims 59-63 and 72-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a transformed monocot plant and a fertile transgenic *Zea mays* plant comprising a recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline.

The claims do not recite the specific identity of any particular recombinant DNA with which the plants have been transformed. Absent reference to the particular identity of the recombinant DNA a critical element of the claimed invention remains undefined, such that the invention is not adequately described. Furthermore, the specification does not describe any plant comprising any recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline. The specification also does not describe any recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline. Given that proline is an amino acid found in virtually all organisms, a variety of structurally and functionally distinct proline biosynthetic enzymes exist that are encoded by genes from divergent plant, animal and microbial species.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lily and Co., 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the

species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Given the claim breadth and lack of description as discussed above, the specification fails to provide an adequate written description of the genus as broadly claimed. Given the lack of written description of the claimed products, any method of using them would also be inadequately described. Accordingly, one skilled in the art would not have recognized Appellants to have been in possession of the claimed invention at the time of filing. See Written Description Requirement guidelines published in Federal Register/ Vol. 66, No.4/ Friday January 5, 2001/Notices: pp. 1099-1111.

Claims 59-63 and 72-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

i) the nature of the invention and the breadth of the claims

The claims are drawn to a transformed monocot plant of any species, encompassing the taxonomically and physiologically divergent species of oat, lily, orchid, palm, onion, turfgrass, asparagus, etc., which is substantially tolerant or resistant to a reduction in water availability, the cells of said plant comprising a recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline, wherein said enzyme is expressed in an amount effective to confer tolerance or resistance to a reduction in water availability. The claims are also drawn to

a fertile transgenic *Zea mays* plant comprising a recombinant DNA encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline.

ii) the content of the disclosure, the existence of working examples, the amount of direction provided by the inventor

The specification does not disclose the identification or isolation of any gene encoding any enzyme involved in proline synthesis, or any plant comprising any recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline. The specification does not provide any guidance for one skilled in the art to determine which recombinant DNA to use and how to express it, because the specification does not disclose any plant tolerant or resistant to a reduction in water availability that comprises any recombinant DNA encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline.

iii) the level of predictability in the art

The ability of a recombinant DNA encoding an enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability is unpredictable. The ability of a proline biosynthetic enzyme to confer tolerance or resistance to a reduction in water availability would be limited by the cellular environment in which the enzyme is expressed. Enzymatic function would be affected by the amount of enzyme expressed, the availability of substrate, and the presence or absence of other factors that might affect enzyme activity or the accumulation of proline.

See, for example, Hu et al. (Proc. Natl. Acad. Sci. USA Vol. 89, pages 9354-9358, October 1992), who teach that the plant proline biosynthetic enzyme Δ^1-pyrroline-5-carboxylate synthetase is subject to feedback inhibition by proline (page 9357 Figure 3). Such feedback

inhibition could limit the ability of a Δ^1-pyrroline-5-carboxylate synthetase transgene to confer tolerance or resistance to a reduction in water availability.

See also, for example, Delauney et al., who teach that multiple enzymes participate in the synthesis of proline in a single biosynthetic pathway in plants and in bacteria, and that proline is also synthesized by two alternative biosynthetic pathways in plants (The Plant Journal, 1993, Vol. 4, No. 2, pages 215-223, page 217 Figures 1 and 2). The participation of multiple enzymes in proline biosynthesis could limit the ability of a single enzyme which catalyzes proline synthesis to produce sufficient proline to confer tolerance or resistance to a reduction in water availability in a plant, since increasing the level of proline in a plant transformed with a transgene encoding a single proline biosynthetic enzyme would depend on the increasing the level of an enzyme that is rate-limiting for proline synthesis. The presence of alternative proline biosynthetic pathways in plants could also limit the ability of a single enzyme which catalyzes proline synthesis to produce sufficient proline to confer tolerance or resistance to a reduction in water availability in a plant, since increasing the level of proline in a plant transformed with a transgene encoding a single proline biosynthetic enzyme would also depend on the amount of enzymatic substrate available, which substrate availability could vary depending on the proline biosynthetic pathway in which the substrate participates. Furthermore, even if proline biosynthesis were increased by the manipulation of one biosynthetic pathway, the proline product produced could act as a feedback inhibitor for the second biosynthetic pathway, so that the total amount of proline produced as the sum of the products of the two pathways might not be sufficient to confer tolerance or resistance to a reduction in water availability in a plant.

Because the ability of a recombinant DNA encoding a single enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability, i.e. to cause proline to accumulate, can be affected by multiple uncontrolled variables, and because different enzymes involved in proline biosynthesis can be affected in different ways by different variables, it is unpredictable whether the expression in a transgenic plant of a recombinant DNA encoding any single unspecified enzyme obtained from any unidentified source that is involved in an unspecified manner in proline biosynthesis would confer tolerance or resistance to a reduction in water availability, i.e. cause proline to accumulate, in a transgenic plant.

iv) the quantity of experimentation required to make or use the invention based on the content of the disclosure

Given the claim breadth, unpredictability and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to identify a multitude of non-exemplified proline biosynthesis enzymes or the genes encoding them from a multitude of sources, to isolate said genes, and to evaluate the ability of a multitude of non-exemplified genes to confer drought tolerance to a multitude of divergent plants transformed therewith.

Claims 61-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 61 is indefinite in the recitation of "increased", as increased is a relative term lacking a comparative basis.

Claim Rejections - 35 USC § 102

Claims 59-61, 63, 72 and 73 are rejected under 35 U.S.C. 102(e) as being anticipated by Verma et al. (U.S. Patent No. 5,639,950, issued June 17, 1997, filed June 29, 1994, having an effective filing date of September 29, 1992).

The claims are drawn to a transformed monocot plant which is substantially tolerant or resistant to a reduction in water availability, the cells of said plant comprising a recombinant DNA encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline, wherein said enzyme is expressed in an amount effective to confer tolerance or resistance to a reduction in water availability, and wherein the transformed plant has an improved osmotic potential when the total water potential of the transformed plant approaches zero.

Verma et al. teach corn, wheat, barley and rye monocot plants comprising a recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase which catalyzes the synthesis of the osmoprotectant proline (column 17 claim 5 and column 18 claim 14). Although Verma et al. do not explicitly teach the amount of Δ^1-pyrroline-5-carboxylate synthetase expression in said plants, the Δ^1-pyrroline-5-carboxylate synthetase expression would necessarily be expressed in an amount effective to confer tolerance or resistance to a reduction in water availability, as the monocot plants taught by Verma et al. are drought resistant. Although Verma et al. do not explicitly teach that the plants have an improved osmotic potential when the total water potential of the transformed plant approaches zero, the plants would necessarily have an improved osmotic potential when the total water potential of the transformed plant approaches zero, as the monocot plants taught by Verma et al. are drought resistant and are transformed with an enzyme which catalyzes the synthesis of the osmoprotectant proline.

Claim Rejections - 35 USC § 103

Claims 59-63 and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Verma et al. (U.S. Patent No. 5,639,950) in view of Rayapati et al. (Plant Physiology, 1989, Vol. 91, pages 581-586) and in light of Appellants' admitted prior art.

The claims are drawn to a fertile transgenic *Zea mays* plant comprising a recombinant DNA encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline, including a recombinant DNA that further comprises a segment encoding an amino terminal chloroplast transit peptide, and a monocot plant regenerated from cells transformed with an expression cassette comprising a recombinant DNA encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline and encoding an amino terminal chloroplast transit peptide.

The teachings of Verma et al. are discussed *supra*.

Verma et al do not teach a DNA segment encoding an amino terminal chloroplast transit peptide.

Rayapati et al. teach that the proline biosynthetic enzyme Δ^1-pyrroline-5-carboxylate reductase (Δ^1-pyrroline-5-carboxylate synthetase) is localized in chloroplasts (page 582 column 2 last paragraph through page 583 column 2 second full paragraph).

Appellants teach that DNA segments encoding amino terminal chloroplast transit peptides were well-known and used in the plant transformation art at the time of Applicant's invention (page 39 lines 7-9).

Given the success of Verma et al. in transforming plants with a recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase which catalyzes the synthesis of the osmoprotectant proline, given the teaching of Rayapati et al. that native Δ^1-pyrroline-5-

carboxylate synthetase is localized in chloroplasts, and given that that DNA segments encoding amino terminal chloroplast transit peptides were known and used in the plant transformation art at the time Appellants' invention; it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to transform a plant with a recombinant DNA encoding both a proline biosynthetic enzyme and a chloroplast transit peptide, give the express purpose of making a transgenic drought-resistant plant transformed with a recombinant DNA encoding both a proline biosynthetic enzyme and a chloroplast transit peptide, without any surprising or unexpected results. Methods for transforming monocots such as maize via electroporation or biolistics were well-known in the art at the time of Appellants' invention, namely August 1993. Accordingly, one of ordinary skill in the art would have been motivated to generate the claimed invention with a reasonable expectation of success. Thus, the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time the invention was made. Seed propagation of desirable genotypes is well known.

(11) Response to Argument

A. Claim Rejections - 35 USC § 112, first paragraph, written description

Appellants note that genes encoding enzymes that elevate the level of proline were known in the art at the time of filing, and point in particular to Verma et al. (U.S. Patent 5,344,923, Exhibit A), cited in the prior art rejection, which discloses the isolation of a mothbean cDNA clone encoding a bifunctional enzyme, delta^{1}-pyrroline-5-carboxylate synthetase, which is involved in the biosynthesis of proline in plants, and Hu et al. (Proceedings National Academy of Science 89:9354-9358; Exhibit B), which discloses a soybean homologue of delta^{1}-pyrroline-5-

carboxylate synthetase, as well as the fact that that the enzyme catalyzes the first two steps in proline biosynthesis in plants. Appellants also point to Verbruggen et al., (Plant Physiol. 103(3):771-81 (Nov, 1993)), who teach that pyrroline-5-carboxylate reductase encodes the enzyme that catalyzes the last step of the proline biosynthetic pathway and who describe the cloning of the corresponding gene from *Arabidopsis*. Appellants further point to additional examples of pyrroline-5-carboxylate reductases that have been described, including a human gene (Dougherty et al. J Biol. Chem., 267 (2), 871-875 (1992)), a yeast gene (Brandriss et al. J Bacteriol. 174 (15), 5176 (1992)), and a pea gene (Williamson and Slocum, Plant Physiol., 1992, 100, 1464-1470). Appellants argue that since the sequences were known to those of skill in the art at the time of filing, Appellants cannot be said to lack written description for these sequences. Appellants also argue that a person of ordinary skill in the art would have known of useful gene sequences involved in the synthesis of proline at the time of Appellants' invention, and that the availability of such gene sequences as common knowledge obviates the rejection under 35 USC 112, first paragraph. (brief pages 4-6)

That some genes encoding enzymes involved in proline biosynthesis were known in the art at the time of filing does not demonstrate that Appellants were in full possession of the claimed genus, or that Appellants' disclosure describes the claimed invention sufficiently to satisfy the written description requirement.

First, the claim limitation "recombinant DNA segment encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline", when considered in isolation, would encompass DNA of any sequence obtained from any source and encoding any enzyme of any type and which catalyzes the synthesis of the osmoprotectant proline. The specification does not

describe or make reference to even a single such DNA segment or enzyme. Furthermore, the prior art of record does not establish that so broad a genus of sequences had been described in the art at the time of filing. Neither Appellants' specification nor the prior art identify any conserved sequences within the broad genus of any proline biosynthetic enzyme or any gene encoding it, wherein such conserved sequences are correlated with the involvement in proline biosynthesis. See MPEP 2163.

Second, the rejected claims are not solely directed to genes encoding enzymes involved in proline biosynthesis. The rejected claims are directed to transformed plants that are substantially tolerant or resistant to a reduction in water availability, the cells of which comprise a recombinant DNA segment encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline wherein the enzyme is expressed in an amount effective to confer tolerance or resistance to a reduction in water availability. Accordingly, the claims require not simply that the genes encode enzymes involved in proline biosynthesis, but the claims additionally require that the genes encode enzymes that have the capacity to be expressed in a plant in an amount effective to confer tolerance or resistance to a reduction in water availability. The specification does not indicate which genes encoding which enzymes would have this capacity.

Third, with respect to Verma et al. (U.S. Patent 5,344,923, Exhibit A) and Hu et al. (Proceedings National Academy of Science, October 1992, 89:9354-9358; Exhibit B), both initially cited by the examiner, as well as Dougherty et al. (J Biol. Chem., 267 (2), 871-875 (1992)) and Brandriss et al. (J Bacteriol. 174 (15), 5176 (1992)), their disclosure of two sequences encoding delta^{1}-pyrroline-5-carboxylate synthetase obtained from mothbean and

soybean and two sequences encoding pyrroline-5-carboxylate reductase obtained from humans and yeast does not serve to adequately describe the claimed invention, because the disclosure of four sequences encoding two type of enzymes involved in proline biosynthesis is not representative of the genus of sequences used to make the claimed transgenic plant, said sequences having been obtained from any source and encoding any enzyme of any type which catalyzes the synthesis of the osmoprotectant proline, and said sequences further encoding enzymes having the capacity to be expressed in a plant in an amount effective to confer tolerance or resistance to a reduction in water availability.

Fourth, with respect to Appellants' citation of Verbruggen et al. (Plant Physiol. 103(3):771-81 (Nov, 1993)), the disclosure of Verbruggen et al. cannot serve to describe the claimed invention because the invention must be described at the time of filing, and Verbruggen et al. was published after the effective filing date of the instant application (August 1993).

Fifth, with respect to Appellants' citation of Williamson and Slocum (Plant Physiol., 1992, 100, 1464-1470), the cited reference is not disclosed in the specification, was not made of record in an information disclosure statement, and was not made of record in previous responses. Since this reference has not previously been considered by the examiner, Appellants' arguments that rely on this reference are considered moot.

B. Claim Rejections - 35 USC § 112, first paragraph, enablement

Appellants assert that the claims are fully enabled by the specification, and specifically assert that, as described in the specification, Appellants' method for transformation of monocots, combined with known examples of enzymes that synthesize the osmoprotectant proline, enables

a person of ordinary skill in the art to produce transgenic monocots that express enzymes that synthesize proline (brief page 6).

The Examiner maintains that the specification does not provide even a single example of an enzyme that synthesizes the osmoprotectant proline, or sequences encoding such enzymes. See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Furthermore, the invention is not limited to transgenic monocots that express enzymes that synthesize proline. The rejected claims are directed to transformed plants that are substantially tolerant or resistant to a reduction in water availability the cells of which comprise a recombinant DNA segment encoding an enzyme which catalyzes the synthesis of the osmoprotectant proline wherein the enzyme is expressed in an amount effective to confer tolerance or resistance to a reduction in water availability. Accordingly, the claims do not simply require that the transgenic monocots express enzymes that synthesize proline. The claims further require that the transgenic monocots express enzymes that have the capacity to be expressed in a plant in an amount effective to confer tolerance or resistance to a reduction in water availability, which implies that expression of the enzymes would additionally result in increased synthesis and accumulation of proline. This requirement is significant in that the enablement rejection is predicated on the unpredictability of the ability of a recombinant DNA encoding a single enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability. Significantly, the specification does not indicate which enzymes involved in the

metabolic pathway that synthesizes the osmoprotectant proline have the capacity to actually increase the synthesis of proline when their activity is increased or introduced, and thereby confer tolerance or resistance to a reduction in water availability, and which do not.

Appellants further point out that the currently claimed invention forms a part of a larger invention comprising use of compatible osmoprotectants in monocots in order to achieve resistance to a reduction in water availability. Appellants point out, for example, that they have illustrated this in the context of transgenic plants that express the osmoprotectant mannitol (see US Patent 5,780,709, Exhibit D) and glycine betaine producing enzymes (see U.S. Patent 6,281,411, Exhibit C) (brief page 6).

With respect to US Patent 5,780,709, Exhibit D, and U.S. Patent 6,281,411, Exhibit C, the Examiner maintains that the cited patents are not germane to the instant rejection because each application is examined on its own merits, because the rejected claims are not directed to the use of recombinant DNA molecules encoding mannitol producing enzymes or glycine betaine biosynthetic enzymes, and because the osmoprotectants mannitol, glycine betaine and proline are distinct compounds that are produced by the activities of different sets of biosynthetic enzymes. The instant enablement rejection is predicated only on the unpredictability of the ability of a recombinant DNA encoding a single enzyme involved in proline biosynthesis to actually confer tolerance or resistance to a reduction in water availability.

Appellants point out that proline, like mannitol and glycine betaine, is a known endogenous osmoprotectant and has long been identified as playing a role in plants under water

deficit. Appellants point in particular to Barnett et al. (Plant Phys., 41:1222, 1966; Exhibit E), who describe that under water deficit, significant increases in certain amino acid pools, such as proline, are observed; to Wyn Jones and Storey (Physiology and Biochemistry of Drought Resistance in Plants, Chapter 9, p. 171-204, Academia Press, Australia, 1981; Exhibit F), who note that increased proline accumulation is observed in barley subjected to water or salt stress; to McCue and Hanson (TIBTECH, 8:358-362, 1990; Exhibit G), who specifically mention the amino acid proline as an osmoprotectant found in diverse organisms; and to Van Rensberg et al. (J. Plant. Physiology, 141:1880194, 1993; Exhibit H), who discuss their observations of increased proline accumulation in drought-resistant tobacco cultivars, where a substantial amount of proline was found to accumulate in the drought-resistant cultivars compared to the drought-sensitive cultivars (brief pages 6-7).

The Examiner does not dispute Appellants' assertion that proline has long been identified as playing a role in plants under water deficit. Furthermore, the Examiner maintains that Appellants' discussion of the role of proline accumulation in plants under water deficit is not germane to the instant enablement rejection, because the rejection is not predicated on the role of proline accumulation in plants under water deficit. The instant enablement rejection is predicated only on the unpredictability of the ability of a recombinant DNA encoding a single enzyme involved in proline biosynthesis to actually confer tolerance or resistance to a reduction in water availability.

Appellants argue that their teaching that increased mannitol and glycine betaine impart water stress tolerance to transgenic monocot plants (see US Patent 5,780,709 Exhibit D and US

Patent 6,281,411 Exhibit C, respectively), and success in using the mtlD gene to impart drought tolerance to a monocot, are therefore indicative of success in overexpressing proline to obtain water stress tolerance. Appellants further argue that together, the knowledge of proline accumulation in plants in response to drought stress, as well as the knowledge of sequences involved in the sequences of proline, demonstrate that the claims were enabled for expressing a proline biosynthesis gene and increased water stress tolerance (brief page 7).

The Examiner maintains that the cited patents teaching that increased mannitol and glycine betaine impart water stress tolerance to transgenic monocot plants are not indicative of success in overexpressing proline to obtain water stress tolerance, because the rejected claims are not directed to increasing mannitol and glycine betaine through the use of recombinant DNA molecules encoding mannitol producing enzymes or glycine betaine biosynthetic enzymes. The rejected claims are also not merely directed to overexpressing proline per se. The rejected claims are directed to increasing proline content in a plant by increasing the expression of proline biosynthetic enzymes by using recombinant DNA molecules encoding proline biosynthetic enzymes to transform plants. The Examiner also notes that the mtlD gene used to impart drought tolerance to a monocot plant encodes an enzyme involved in mannitol biosynthesis, not proline biosynthesis. The use of the mtlD gene to impart drought tolerance to a monocot plant is therefore not relevant to the enablement of the rejected claims, as mannitol and proline are distinct compounds that are produced by the activities of different sets of biosynthetic enzymes. The Examiner further maintains that the specification provides no guidance with respect to which sequences involved in the synthesis of proline to express in a transformed plant in order to increase proline content and water stress tolerance.

Appellants additionally point out that the Examiner's own prior art rejection states that expression of a delta[1]-pyrroline-5-carboxylate synthetase would inherently result in water stress tolerance, and Appellants argue that given that the transformation methods and expression vectors illustrated in Appellants' working examples are fully enabled for monocot transformation and heterologous expression with osmoprotectant genes, it is respectfully submitted that the claims must be held enabled in view of the Examiner's assertion. Appellants further argue that while legally flawed from an inherency rejection standpoint because the cited references are not enabling for transgene expression in maize, and the insufficiency of Verma as of its effective date, the art rejection affirmatively acknowledges the enablement of the claims given Appellants' enablement of transgene expression in monocots (brief page 7).

The Examiner does not dispute that Appellants are generally enabled for monocot transformation and heterologous gene expression in monocotyledonous plants. However, the claims are not directed to mere heterologous gene expression in monocotyledonous plants, or to the mere expression of delta[1]-pyrroline-5-carboxylate synthetase in monocotyledonous plants. The rejected claims are directed to transformed monocot plants that are substantially tolerant or resistant to a reduction in water availability the cells of which comprise a recombinant DNA segment encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline wherein the enzyme is expressed in an amount effective to confer tolerance or resistance to a reduction in water availability. Accordingly, the claims do not simply require that the transgenic monocots plants express a heterologous gene. The claims further require that the transgenic monocots express enzymes encoded by heterologous genes wherein the enzymes have the capacity to be expressed in a plant in an amount effective to confer tolerance or resistance to a

reduction in water availability, which implies that expression of the enzymes would additionally result in increased synthesis of proline. Furthermore, the instant enablement rejection is not predicated on the availability or predictability of methods for expressing a heterologous gene in monocotyledonous plants. The instant enablement rejection is predicated on the general unpredictability of the ability of a recombinant DNA encoding an enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability to a transgenic plant, i.e. to result in increased synthesis and accumulation of proline in a transgenic plant. Accordingly the Examiner's assertion that a monocot transformed with the delta^{1}-pyrroline-5-carboxylate synthetase gene would inherently have a resistance to water availability is not tantamount to acknowledging the enablement of the rejected claims, because the rejected claims are not limited to a monocot transformed with the delta^{1}-pyrroline-5-carboxylate synthetase gene, and because the enablement rejection is predicated on the general unpredictability of the ability of a recombinant DNA encoding a single enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability to a transgenic plant. In this regard the Examiner also notes that none of Appellants' working examples exemplify the effect of expressing in monocots heterologous genes encoding even the single enzyme delta^{1}-pyrroline-5-carboxylate synthetase, or the effect of expressing in monocots heterologous genes encoding any other enzyme involved in proline biosynthesis. With respect to the allegedly inconsistent rejections under 35 U.S.C. 112 and 35 U.S.C. 103, the Examiner maintains that the test for adequacy of a prior art disclosure to anticipate or render claims obvious is not the same test as that for adequacy of a patent application disclosure to support claims under 35 U.S.C. 112, as taught in In re Hafner, 161 USPQ 783, (CCPA 1969).

C. Claim Rejections - 35 USC § 112, second paragraph

Appellants reiterate the text of claim 61, with emphasis on its recitation of the term "increased". Appellants argue that the meaning of the term "increased" is clear to one of skill in the art, particularly when taken in combination with the teaching in the specification, and that a plain reading of the claim indicates that the enzyme is increased relative to a Zea mays plant that lacks the recombinant DNA segment. Appellants assert that no other logical reading can be made of the claim given the text of the claim, and that the Examiner has failed to point to any other reasonable meaning that could be given. Appellants further assert that there is no indefiniteness in using a relative term that has a comparative basis, and that all that is required under the second paragraph of 112 is that one of skill in the art understand the metes and bounds of the claim when read in context and in view of the specification, and that claim terms must be read together with the claim as a whole and in view of the understanding of those of skill in the art (brief pages 8-9).

The Examiner maintains that "increased" is a relative term, and that the rejected claim recites no comparative basis for this term. Claims 61, directed to a fertile transgenic *Zea mays* plant, recites that the first DNA segment is expressed so that the level of the enzyme is increased in the transgenic *Zea mays* plant. The Examiner does not dispute that a plain reading of the claim could indicate that the enzyme is increased relative to a *Zea mays* plant that lacks the recombinant DNA segment. When taken in combination with the teaching in the specification, however, a plain reading of the claim could also indicate that the enzyme is increased relative to the level of the endogenous enzyme in the transgenic *Zea mays* plant, or relative to the level of the enzyme produced under non-stress conditions, since the specification does not specifically

explain in what way the level of an enzyme which catalyzes the synthesis of the osmoprotectant proline would be increased, and since the specification indicates that one of the mechanisms employed by nontransgenic water deficient-tolerant plants to grow and yield is osmotic adjustment thorough the increased synthesis of osmoprotective metabolites such as proline. Because the rejected claim recites no comparative basis for "increased", and because "increased" could reasonably be interpreted in more than one way when taken in combination with the teaching in the specification, the Examiner maintains that claim 61, and claims 62-63 dependent thereon, are indefinite in the recitation of "increased".

E. Claim Rejections - 35 USC § 102

Appellants first point out that they noted in their response to the first Office Action that the current application claims priority to August 25, 1993 as a divisional application of U.S. Application Serial No. 08/599,714, filed January 19, 1996 (now U.S. Patent No. 6,281,411), which application was a continuation-in-part application of currently pending U.S. Application Serial No. 08/113,561, filed August 25, 1993, and that this grandparent application disclosed that transgenic monocot plants with drought resistance, including maize, can be prepared by expressing genes encoding a variety of osmotically active metabolites including proline. Appellants argue that the Verma II patent is effective only as of its June 1994 filing date for disclosure of "corn" and thus cannot anticipate the current claims. Appellants further argue that Verma I, on which the examiner relies for an effective filing date of September 29, 1992, is insufficient, since a full text search of the Verma I patent on the USPTO patent database reveals

that this patent does not include the terms "maize", "Zea mays" "corn" or "monocot" (brief pages 9-10).

Appellants' response to the first Office Action indicating that the current application claims priority to August 25, 1993 is acknowledged and is not disputed. Appellants' assertion that the Verma I patent does not include the terms "maize", "Zea mays" "corn" or "monocot" is also acknowledged and is also not disputed.

The Examiner maintains, however, that the Verma II patent is effective as of the filing date of its parent application for its claims directed to transgenic plants, including transgenic corn plants, because there is no substantial difference between the disclosure of the Verma II patent and the disclosure of its parent with respect to making and using plants transformed with a recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase. The Verma I patent discloses a recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase obtained from mothbean (Figure 1), and transgenic mothbean plants comprising said recombinant DNA, said transgenic plants exhibiting a 10 to 100 fold increase in proline in root tissue as compared to nontransformed wild-type plants (column 5 line 18-58). The Verma I patent claims recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase (columns 13-14). The Verma II patent discloses additional data pertaining to the same transgenic mothbean plants disclosed in the Verma I patent (column 6, line 47 through column 9, line 29 of Verma II); the disclosure of the Verma II patent regarding the method of obtaining transformed plants (column 6, lines 9-45 of Verma II) is IDENTICAL to the disclosure of Verma I (column 5, lines 18-46) regarding the method of obtaining transformed plants. The Verma II patent claims methods of transforming plants to increase salt tolerance and drought resistance, as well as explicitly claiming transformed

plants, including transformed corn plants (columns 17-18 Verma II). Because there is no substantial difference between the disclosure of the Verma II patent and the disclosure of its parent with respect to making and using plants transformed with a recombinant DNA encoding Δ^1-pyrroline-5-carboxylate synthetase, the Verma II patent claims directed to transgenic plants, including transgenic corn plants, are accorded the effective filing date of the parent application.

Appellants further argue that the rejected claims are drawn to a transgenic monocot plant which is substantially tolerant or resistant to a reduction in water availability, where the transgenic plant comprises a transgene encoding an enzyme catalyzing the synthesis of proline, whereas Verma I merely discloses the sequence of delta^1-pyrroline-5-carboxylate synthetase, making the sequence available to those of ordinary skill in the art who might discover a use for it, e.g., as Appellants have discovered a use in producing transgenic monocots expressing proline for drought resistance (brief page 10).

The Examiner maintains that the disclosure of Verma I is not limited to the disclosure of the sequence of delta^1-pyrroline-5-carboxylate synthetase. Verma I also discloses transgenic mothbean plants comprising said recombinant DNA, said transgenic plants exhibiting a 10 to 100 fold increase in proline in root tissue as compared to nontransformed wild-type plants (column 5 line 18-58). Verma I additionally discloses that it would be desirable to use genetic engineering of the proline production pathway in plants to counter osmotic stress to alter the level of a known osmoprotectant to thereby lead to a significant enhancement of crop performance under conditions of salt and drought stress (column 1 lines 43-48), that one object of the invention is to provide a method to overproduce proline and thus increase sodium chloride and drought

resistance in a plant by the introduction into the plant of the P5CS (delta[1]-pyrroline-5-carboxylate synthetase) cDNA (column 2 lines 7-13), that regulation of the proline synthesis pathway in plants is exerted primarily at the P5CS step (column 4 lines 49-53), and that the invention demonstrates that it is possible to remove feedback control on proline production in plants and to produce the overexpression of proline from P5CS to confer salt and drought tolerance on a crop plant (column 5 lines 53-58). Furthermore, the Examiner maintains that Appellants have not discovered a use for the delta[1]-pyrroline-5-carboxylate synthetase sequence, as Appellants' specification makes no reference to this enzyme, or to any sequence that encodes it.

With regard to the Examiner's statement that plants disclosed by Verma I and/or II would inherently be substantially tolerant or resistant to a reduction of water availability, Appellants note that this statement directly contradicts the enablement rejection. Appellants argue that the Examiner cannot have it both ways, and that in view of the comment by the Examiner admitting that a monocot transformed with the delta[1]-pyrroline-5-carboxylate synthetase gene would inherently have a resistance to water availability, Appellants submit that the Examiner has acknowledged the enablement of the claims (brief page 11).

Appellants' arguments directed to the rejection of the claims under 35 USC 112, first paragraph, are not germane to the instant rejection of the claims under 35 USC 102, as the different sections of the statute impose different requirements. See Hafner cited above. Furthermore, the statement that plants disclosed by Verma I and/or II would inherently be substantially tolerant or resistant to a reduction of water availability does not contradict the enablement rejection, because the rejected claims are not directed to transformed plants which

comprise a recombinant DNA segment encoding a delta[1]-pyrroline-5-carboxylate synthetase gene, and because the enablement rejection under 35 USC 112 was not solely predicated on the unpredictability of the ability of a recombinant DNA encoding delta[1]-pyrroline-5-carboxylate synthetase to confer tolerance or resistance to a reduction in water availability. The rejected claims are directed to transformed monocot plants that are substantially tolerant or resistant to a reduction in water availability, the cells of which comprise a recombinant DNA segment encoding any enzyme which catalyzes the synthesis of the osmoprotectant proline, and enablement rejection under 35 USC 112 was predicated on the general unpredictability of the ability of a recombinant DNA encoding an enzyme involved in proline biosynthesis to confer tolerance or resistance to a reduction in water availability. Accordingly the Examiner's assertion that a monocot transformed with the delta[1]-pyrroline-5-carboxylate synthetase gene would inherently have a resistance to water availability is not tantamount to acknowledging the enablement of the rejected claims. Furthermore, the instant specification does not even enable the production of maize plants transformed with ANY gene encoding ANY proline biosynthetic enzyme, while Verma I and II are indeed enabling for such transformed plants, as discussed above.

Appellants further argue that the Examiner's conclusion regarding inherency is flawed, as the Examiner has failed to provide any objective basis to support the enablement of the Verma I or Verma II reference. Appellants point out that the Examiner has failed to show that Verma I and/or II disclose a method for transforming monocots and teach transformation vectors that could be used to achieve gene expression in monocots. Appellants further argue that the

Examiner's unsupported allegations do not meet the relevant legal standards or the standards of the APA for maintaining a rejection, and that the Examiner is not allowed to bootstrap deficient references to support an anticipation rejection through unsupported allegations of inherency (brief pages 11-12).

The Examiner's conclusion regarding inherency is not flawed, and the Examiner has provided objective basis to support the enablement of the Verma I and II. First, as discussed above, and at page 10 of the office action mailed September 9, 2003, Verma I and/or II need not disclose a method for transforming monocots and teach transformation vectors that could be used to achieve gene expression in monocots, because both Verma I and Verma II are enabled for the transformation of monocots, since the transformation of monocots was known in the art at the time of filing of Verma I.

Second, with respect to the Examiner's assertion that a monocot transformed with the delta^{1}-pyrroline-5-carboxylate synthetase gene would inherently have a resistance to water availability, as discussed above, and at page 10 of the office action mailed September 9, 2003, Verma I discloses transgenic plants comprising a recombinant DNA encoding Δ^{1}-pyrroline-5-carboxylate synthetase (column 5 first full paragraph and Table 1), and Verma I teaches the use of Δ^{1}-pyrroline-5-carboxylate synthetase to increase proline content in transgenic plants as a means of enhancing osmotic stress tolerance (column 1 through column 2 fourth paragraph; column 5 second full paragraph). Furthermore, the transgenic plants disclosed in Verma I exhibit a 10 to 100 fold increase in proline in root tissue as compared to nontransformed wild-type plants (column 5 Table 1). Finally, Verma II discloses additional data pertaining to increased salt tolerance and drought resistance of the same transgenic plants disclosed in Verma I (column 6,

line 47 through column 9, line 29 of Verma II), and claims methods of transforming plants to increase salt tolerance and drought resistance, as well as transformed plants, including transformed corn plants (columns 17-18). It is not within the purview of the Examiner to judge the validity of issued claims in a U.S. patent.

F. Claim Rejections - 35 USC § 103

Appellants note that all elements of the claims have not been shown in the art and maintain that the rejection is insufficient on its face. Appellants argue that the Examiner has failed to show monocot plants in the prior art. Appellants maintain that the Examiner's assertion that Verma et al. teach corn, wheat, barley, and rye monocot plants comprising a recombinant delta^{1}-pyrroline-5-carboxylate synthetase gene that catalyzes proline synthesis is unsupported and is baseless given that Verma does not even reference maize or monocot plants as of its effective prior date. Appellants also argue that Verma II has not even been demonstrated by the Examiner to be properly used as prior art. Appellants further argue that while Verma II claims a number of transgenic plant types, including maize, the reference does not disclose an actual transgenic monocot plant and thus does not cure the defect of Rayapati et al. Appellants further argue that the combined references do not teach fertile, transformed corn, and have not even been shown to motivate a person of ordinary skill in the art to attempt to transform corn, let alone provide a reasonable expectation of success in doing so (brief pages 12-13).

The Examiner maintains that Verma II teaches corn, wheat barley, and rye monocot plants comprising a recombinant delta^{1}-pyrroline-5-carboxylate synthetase gene that catalyzes

proline synthesis, and, as discussed above, that the Verma II patent claims directed to transgenic plants, including transgenic corn plants, are accorded the effective filing date of the parent application. This assertion is neither unsupported nor baseless, because Verma II in fact claims corn, wheat barley, and rye monocot plants comprising a recombinant delta^{1}-pyrroline-5-carboxylate synthetase gene (column 18 claims 13-16), including corn, wheat, barley, and rye monocot plants with increased drought resistance and increased proline production (column 18 claims 14 and 15), and the claims of a U.S. patent are presumed to be valid. Furthermore, as discussed above, the Examiner maintains that both Verma I and Verma II are enabled for the transformation of monocots, because the transformation of monocots, including corn, was known and practiced in the art at the time of filing of Verma I. Finally, the Examiner maintains that Rayapati et al. would motivate one of ordinary skill in the art to transform a plant with a recombinant DNA encoding both a delta^{1}-pyrroline-5-carboxylate synthetase and a chloroplast transit peptide, because Rayapati et al. teach that native delta^{1}-pyrroline-5-carboxylate synthetase is localized in chloroplasts, and because DNA segments encoding amino terminal chloroplast transit peptides were known and used in the plant transformation art at the time of Appellants' invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Cynthia Collins
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Cynthia Collins 3/15/05

Conferees
David Fox, Primary Patent Examiner
Amy Nelson, Supervisory Patent Examiner
Bruce Campell, Supervisory Patent Examiner

SCHWEGMAN, LUNDBERG,
WOESSNER & KLUTH, P.A.
P.O Box 2938
Minneapolis, MN 55402

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638

Amy Nel

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Bruce Campell

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600